ORIGINAL RESEARCH

Physicochemical Evaluation of Brands of Amlodipine Besylate Tablets

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ABSTRACT

Background: Hypertension is a chronic condition, and the cost of filling prescriptions has a potential of putting a financial strain on patients, hence the need for lower priced but bioequivalent generics. The Nigerian drug market is awash with generics of Amlodipine besylate, a first line drug in the treatment of hypertension, therefore, any prescribed alternative must be bioequivalent to the originator.
Objectives: This study assessed the physicochemical properties of some brands in order to predict pharmaceutical and bioequivalence and invariably, the interchangeability with the innovator brand.
Methods: Compendial parameters of average weight, friability, disintegration, drug content and dissolution profile of ten generic brands were evaluated using the United States Pharmacopeia (USP) as well as the non-official hardness test.
Results: Two brands failed the test for hardness, while still keeping to the stipulated friability limit. All the brands met the required disintegration time, irrespective of the discordance of some brands in the breaking force and friability values. All brands were found to contain between 92.00 and 103.57% (w/w) of Amlodipine besylate. Two brands failed to achieve ≥75% dissolution expected at 30 minutes and this was reflected in the low f_2 values of 35.06% and 28.73%. The dissolution curves displayed a similarity for two brands, which was also corroborated by the high percentage dissolution efficiency (DE) of 92.00%, as well as the f_1 and f_2 values, compared to the innovator brand.
Conclusion: Although the parameters used may predict therapeutic equivalence, interchangeability with the comparator brand is subject to relevant bioequivalence studies.

Keywords: Amlodipine, Dissolution profile, Dissolution efficiency, Hypertension, Disintegration

INTRODUCTION

Hypertension, a condition of a protracted rise in blood pressure (BP ≥ 140/90), is a foremost factor in cardiovascular disease and over time, results in end-organ damage[1]. Essential hypertension occurs when the body's compensatory mechanisms can no longer maintain the balance in blood pressure[2]. With a prevalence rate of 1.13 billion people globally, it is no surprise that hypertension is the primary cause of premature death globally and Africa is the highest contributor of the global disease burden (27%)[3]. Studies showing evidence of a particularly high overall prevalence in

urban Nigeria of 27.5% - 30.6%, put about a third of these adults at risk; men more so than women[4,5].

Amlodipine belongs to the class of antihypertensives referred to as dihydropyridine calcium channel blockers (CCBs). They act by binding to L-type calcium channels in the vascular smooth muscle, causing muscle relaxation and result in vasodilatation and a subsequent decrease in blood pressure. They are recommended as the first line drug in adults aged 55 and above as well as in black African or African-Caribbean patients without type 2 diabetes[6]. Amlodipine is classified as an essential medicine[3] and has numerous generic brands. The economic strain from the use of medication for the management of hypertension, expectedly, leads to a decline in the prescription and use of fixed dose combination medications (or brand-name drugs), in favour of individual generic medications to save cost[7]. There are also studies indicating a positive correlation between the lower cost of generics (compared to innovator brand) and drug compliance[8].

A generic drug is intended to match the innovator drug in dose, safety, strength, route of administration, quality, and efficacy. They sometimes leverage on the established animal and clinical (human) studies of the innovator medicines to validate safety and effectiveness and so are relatively lower in cost. In addition, the approval of several generic drugs in lieu of a single product further increases competition in the marketplace and lowers prices[9].

Bioequivalence studies, which evaluate the effectiveness of generic brands of medicines, have remained a focus of academic research and the results of several of these comparative studies to a single innovator brand have formed the basis of medicines regulation and in WHO prequalification[10]. The recommended assessment guidelines support individual countries in generating their policies and market structures that influence generic substitutions, resulting in recent times to an increase in the use of generics across many countries[11].

Proper registration by the relevant national drug agencies notwithstanding, the quality and interchangeability of marketed multisource drug products still pose a problem to establish, given the rate of entry of new and sustainability of older generic brands in the Nigerian drug market. This problem plagues many developing countries and Nigeria is not spared, as the drug market is awash with a variety of generic brands of Amlodipine Besylate. This proliferation of imported generics may make it harder for the community pharmacist to make an informed decision about the efficacy of any particular generic brand comparative to the innovator brand. The continuous and proper monitoring of the ever-increasing number of generics in the system therefore is imperative. Similar studies have assessed the quality control parameters of some commercially available generics of Amlodipine Besylate in the Nigerian drug market at the time[12,13]. However, in the present study, the prevailing market brand composition have been analyzed and the results obtained used as predictive measures of bioequivalence and interchangeability between select current market brands and innovator drug.

In this study, we compared nine different brands of Amlodipine besylate tablets (10 mg) obtained from selected pharmacy outlets on Lagos Island, Nigeria with the innovator brand, using various official and non-compendial parameters for quality assessment and as a predictor of bioequivalence and interchangeability between various generics.

MATERIALS AND METHODS

Equipment:

Analytical Weighing Balance (Mettler Toledo®, USA); Mechanical Hardness Tester (Monsanto, Germany); Tablet Friability Tester (Erweka-Apparatebau®-GMBH, Heusenstamm, Germany); Disintegration apparatus serial number

065785 (Copley Erweka-Apparatebau, Germany); Dissolution apparatus, USP (ELECTROLAB TDT-08L, N. J, USA); HPLC (Agilent 1200, USA); Ultraviolet/Visible Spectrophotometer (J.P. SELECTA, Spain); pH meter (Hanna instruments, HI 3220, USA); Sonicator (J.P. SELECTA, 577001, Spain). All equipment was appropriately qualified and calibrated prior to the analyses.

Materials

The amlodipine besylate reference standard (99.57% of purity) was courtesy gift from the Drug Quality Control Laboratory, Lagos State University Teaching Hospital. Ten different brands of commercial amlodipine besylate tablets with labeled strength of 10mg. All samples used were within the shelf-life as stated by their manufacturers and as required by the current legislation. Methanol 99.9% purity (LiChrosolv®, 67-56-1, Germany), Acetonitrile 99.9% purity (LiChrosolv®, 75-05-8, Germany), Triethylamine 99% (LobaChemie pvt.limited), Hydrochloric acid 37%, Phosphoric acid 85% (BDH chemicals LTD., Poole, England). All reagents used were of analytical grade.

Drug Sampling:

The different brands of amlodipine studied were selected based on frequency and volume of importation and availability in community pharmacies. The samples were randomly purchased from pharmacies located in Idumota area of Lagos state.

All the brands used were registered by the National Agency for Food and Drug Administration and Control (NAFDAC), Nigeria, and were analyzed at least six months prior to their expiration date. After purchase, information on the manufacturer's address and country of origin of the brands, batch numbers, manufacturing dates, label strength, and registration status by NAFDAC were extracted from the product label where available (Table 1). The different brands were coded as AML 01–10, with the innovator brand being AML 01.

Methods:

The different brands were subjected to various compendial and non-compendial physical tests. The compendial tests: uniformity of weight, friability, disintegration, dissolution and drug content; were carried out as described in the USP[14]. Hardness was also carried out as a non-compendial test.

Weight Uniformity Test:

Twenty tablets of each brand were randomly selected and weighed individually on an analytical weighing balance and the individual tablet weights were recorded. The average weight of the tablets and percentage deviation of individual tablets from the mean were calculated and recorded based on the method specified in the USP[14].

Hardness Test:

The force needed to break a tablet in a compression test was evaluated by placing each of the 10 randomly selected tablets of each brand of amlodipine in a vertical position between the jaws of the mechanical hardness tester with respect to the direction of application of the force. This force was calculated as average tablet hardness ±SD and expressed in kgF[15].

Friability Test

Randomly selected (ten) whole tablets of each brand of Amlodipine besylate were carefully weighed together and the collective weight was recorded. The weighed tablets were placed in the rotating wheel of the friability tester and allowed to rotate for 4 minutes at 25 rpm. The tablets were removed from the rotating wheel, carefully de-dusted and re-weighed to obtain the final weight. The difference between the final and initial weights of the tablets was calculated as the percentage friability[14].

Disintegration Test

The disintegration time test for each sample was done by placing one tablet out of the six randomly selected tablets in each of the six tubes of the apparatus and the basket rack

placed in approximately 500 mL of distilled water, at about 37 ± 1.0 ºC and such that the tablets remain 2.5 cm below the surface of the liquid. The average time taken for all the tablets to break up into granules was noted and recorded[14].

Content determination of the tablets

Quantitative assay of the different brands of amlodipine besylate tablets was carried out according to the High-performance Liquid Chromatography (HPLC) method described in the USP (2014), with slight modifications. The liquid chromatograph was equipped with a pump, Model 1200 Infinity series, Agilent HPLC and a UV detector set at 239 nm. Separation was carried out using a Waters Xterra C18 column (4.6 x 150 mm, 5 µm) at a flow rate of 1 mL/min and column temperature was set at 40 °C. The mobile phase consisted of methanol, acetonitrile, and buffer in a ratio of 35:15:50. The buffer was prepared by adding 7 mL of triethylamine to 900 mL of distilled water and the solution was adjusted to a pH of 3 with phosphoric acid. Standard stock solution, 0.2 mg/mL, of amlodipine besylate reference standard was prepared with the mobile phase and used in preparing the working solution, 0.02 mg/mL. Twenty randomly selected tablets from each brand were weighed, pulverized and 50 mg equivalent of amlodipine besylate was weighed, dissolved in the diluent to obtain 0.2 mg/mL sample stock solution and filtered. The filtered solution was diluted to obtain 0.02 mg/mL working solution. Equal volume (50 µL) of the standard and sample solutions were separately injected into the chromatograph under the same conditions. The concentrations of amlodipine in the sample solutions were determined from the peak responses obtained relative to that of the peak responses of the reference standard and the percentage purity of the samples determined.

Dissolution Assay:

Dissolution test was carried out using a USP apparatus 2 (Paddle type)[14]. The medium was 500 mL of 0.01 N hydrochloric acid, at a rotated fixed speed of 75 rpm, and the temperature was maintained at 37 ± 0.5 ºC. Six tablets selected randomly from each brand were used for the test. From each vessel, 5 mL solutions were withdrawn, from an area about midway between the surface of the dissolution medium and the top of the rotating paddle at specified time periods of 5, 10, 30, 45, and 60 mins. The withdrawn solutions were replaced by a fresh dissolution medium, 5 mL, to maintain the sink volume. Each solution was then filtered using a 0.45 µm millipore filter, diluted and analysed with UV-visible spectrophotometer at λ_{max} 239 nm as the standard.

Standard stock solution, 100 µg/mL of amlodipine besylate reference standard was prepared with the dissolution medium and used in preparing working solutions (1, 2, 4, 5, 10, 20 and 30 µg/mL). The absorbance of the standard working solutions was measured at λ_{max} 239 nm using UV-visible spectrophotometer and used for preparing calibration curve. The concentrations of amlodipine besylate were obtained using their absorbance and the regression equation from the calibration curve of amlodipine standard. The dissolution profiles of the ten brands were obtained and the fit factors: difference factor (f_1) and similarity factor (f_2) between the dissolution profiles of the generic brands AML 02–10 in comparison to the innovator brand AML01 were calculated[16].

Statistical analysis:

The average of the sample results was compared by paired Student's t-test, using Microsoft Excel. The regression and linear correlation analysis were performed by the least-square method, using the same software. Statistical significance was considered if $p \leq 0.05$. The dissolution efficiency (DE) was calculated at 60 mins from the area under the dissolution curve between time points t_1 and t_2 (measured using the trapezoidal rule), expressed as a percentage of the curve at maximum dissolution, y_{100}, over the same

time period and y is the percentage of dissolved product[17].

$$DE = \frac{\int_{t_1}^{t_2} y dt}{y_{100} \times (t_2 - t_1)} \times 100$$

A comparison of the dissolution profiles used the similarity and difference factor equations below

$$f_2 = 50 \cdot \log\left\{\left[1 + \left(\frac{1}{n}\right)\sum t = 1^n (R_t - T_t)^2\right]^{-0.5} \cdot 100\right\}$$

$$f1 = \left\{\frac{[\Sigma |Rt\text{-}Tt|]}{[\Sigma[Rt]}\right\} \times 100$$

Where: R_t = Average percentage of reference drug dissolved at time (n); T_t = Average percentage of test drug dissolved at time (n). Dissolution profiles were considered similar if $f_2 \geq 50$.

RESULTS

The physicochemical properties evaluated include average weight, hardness, % friability and disintegration time (Table 2). The percentage drug content and dissolution profile are presented in Table 3. The average weights (Table 2) of the different brands varied widely from 414.31 ± 0.89 mg (AML 02) to 172.94 ± 1.86 mg (AML 04).

Table 1: Some Label Information on the Brands of Amlodipine Tablets Evaluated

NAFDAC Number	Code	Country of Origin	Batch Number	Labelled Strength	Production Date	Expiration Date
04-5354	AML 01*	Germany	3761	10 mg	Jun-16	May-20
B4-6860	AML 02	India	3510	10 mg	Mar-18	Feb-21
B4-6505	AML 03	India	S798150	10 mg	Jul-18	Jun-21
A4-9400	AML 04	India	LO1801	10 mg	Aug-18	Jul-21
B4-6762	AML 05	India	A18621	10 mg	Oct-18	Sep-21
A4-9400	AML 06	India	AMLT 1803	10 mg	May-18	Apr-21
A4-7895	AML 07	China	180709	10 mg	Jul-18	Jul-21
A4-2059	AML 08	Nigeria	22	10 mg	Oct-17	Sep-20
A4-3426	AML 09	India	AF63803	10 mg	May-18	Apr-21
B4-679	AML 10	India	TE7113	10 mg	Apr-17	Mar-20

*Innovator brand

The weight variation tolerance for tablets differs depending on average tablet weight. As stipulated in the USP (2014), not more than two of the twenty individual weights should deviate from the average weight by more than 7.5%, for tablets weighing 130 – 324 mg and not more than 5% for tablets above 324 mg. All the tablets satisfied the pharmacopeial standards as outlined above and the variances in weight were not statistically significant ($p < 0.05$).

The structural integrity of the tablets was evaluated by measuring the breaking force for the tablets. The tablet hardness range of all brands had a mean upper limit of 7.50±0.55 KgF (AML 06) and a lower limit of 1.73±0.20 KgF (AML 02). The allowable limit of the breaking force of uncoated tablets is ≥4 KgF[14], thus according to this test, only two of the brands, AML 02 (1.73±0.20) and AML 04 (3.20±0.16) failed to meet the minimum force required. The resulting friability of the tablets, expressed in percentage values, were between 0.01 (AML 05) and 0.41% (AML 09). A maximum weight loss of not more than 1.0% is considered acceptable for most products, therefore, all brands of Amlodipine tablet used met the pharmacopeial set standards.

All selected brands of Amlodipine tablets disintegrated between 0.06 (AML 01) and 5.27 (AML 08) minutes of the test. This implies that they were all within the limits considered suitable according to USP

standard, since a maximum of 15 minutes is allowable for the complete disintegration of uncoated tablets.

Table 2. The Physicochemical parameters of the brands of Amlodipine tablets.

Samples	Mean weight (mg)±RSD	Mean hardness (kgf) ± SD	Percentage friability	Mean disintegration time (min:sec) ±SD
AML 01	414.05±0.89	7.28±0.42	0.03	0:06±0:01*
AML 02	414.31±1.25	1.73±0.20	0.04	1:03±0:06
AML 03	355.41±1.92	4.13±0.24	0.24	0:16±0:00*
AML 04	172.94±1.86	3.20±0.14	0.09	0:50±0:05*
AML 05	220.91±0.89	4.60±0.42	0.01	2:17±0:13
AML 06	189.06±2.26	7.50±0.55	0.35	0:37±0:10
AML 07	247.25±2.83	5.40±0.22	0.02	0:56±0:06
AML 08	186.04±4.19	4.10±0.64	0.21	5:27±1:02
AML 09	335.20±1.46	6.98±0.85	0.41	0:25±0.00*
AML 10	352.23±1.29	5.75±0.70	0.21	2:48±0:10

Values represent physicochemical properties of the Amlodipine tablet brands. Each value represents the mean ± standard deviation (SD). Statistically significant differences between the brands, *$p \leq 0.05$

Dissolution Assay

The dissolution profiles of the ten selected brands of amlodipine besylate tablets are as presented in Figure 2. The *in vitro* drug release profile showed a variability among the different brands, with the highest release by AML 09 (84.60 %). It also showed that all other brands except AML 08 and AML 10 released up to 75 % of the labelled strength within 30 mins, as stipulated in the USP (2014). The outcome of analysis for amlodipine besylate content in the different brands using HPLC (Table 3) ranged from 92.00 to 103.57 %, also conforming to the USP specification that stipulates a range of 90 - 110 %.

Two predictors of bioequivalence - dissolution efficiency (DE) of the tablets at 60 minutes and fit factors (f_1 and f_2) are depicted in Table 3. The highest DE (93 %) was exhibited by the innovator brand AML 01 and the lowest DE (66 %) was by AML 10 for the same time period. The fit factors, as calculated, are another model-independent method of comparing dissolution profiles of test and reference formulations. Values for difference factors f_1 less than 15 and similarity factors f_2 values greater than 50 suggest a parallel between dissolution curves. In this study, the calculated f_1 values for AML 08 and AML 10 were high at 26.00 and 39.58 respectively, while the similarity factors were 35.06 and 28.73 respectively in comparison to the innovator brand AML 01. All other brands had values within the acceptable range, with AML 09 giving the highest f_2 value (79.79) and showed similarities in the dissolution curve with the innovator brand.

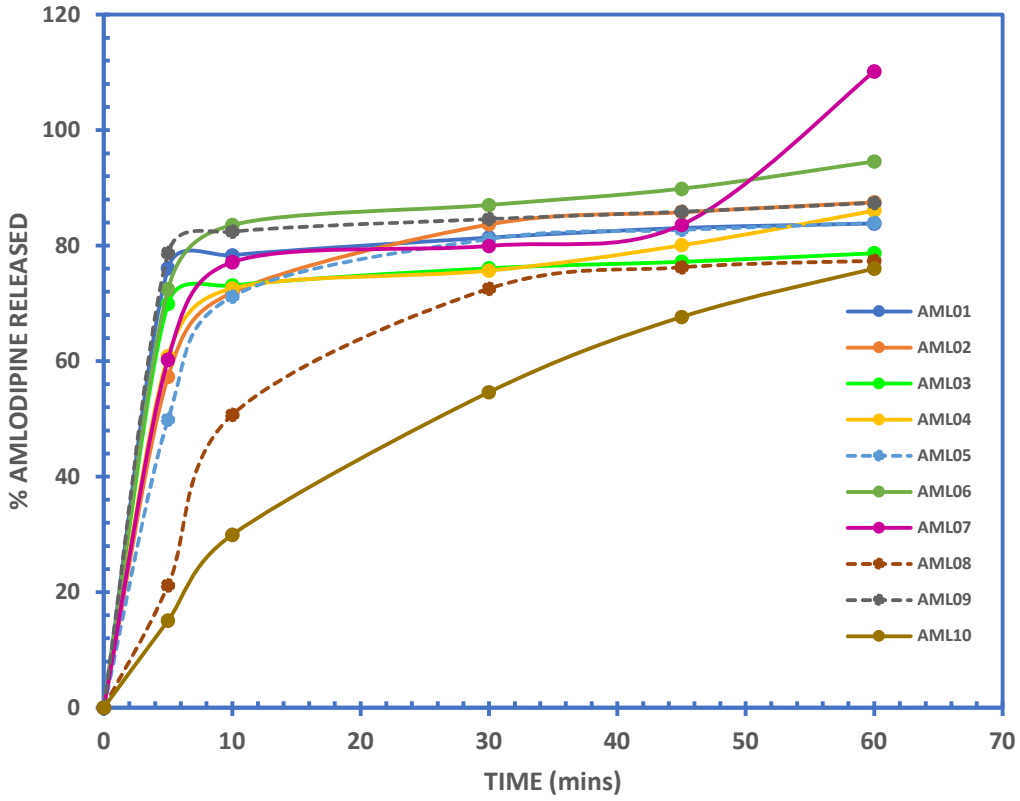

Figure 2. Dissolution profiles of amlodipine besylate tablets (Innovator Brand: AML 01 and Brands AML 02 to AML 10)

Table 3. The dissolution efficiency, drug content and fit factors of the brands of amlodipine besylate

Brand code	Amount released at 30 min (%)	Drug content (%)	f_1	f_2	DE at t_{60}
AML 01	81.37	98.33	-	-	93
AML 02	83.66	94.00	8.43	59.11	87
AML 03	76.07	103.30	6.88	69.62	92
AML 04	75.67	95.30	7.91	62.33	85
AML 05	81.14	92.00	8.45	53.12	88
AML 06	87.04	103.57	7.97	65.31	88
AML 07	79.95	98.03	11.26	50.48	72
AML 08	72.56	101.06	26.00	35.06	80
AML 09	84.60	99.34	4.04	79.79	92
AML 10	54.63	97.08	39.58	28.73	66

Key: Difference factor (f_1), similarity factor (f_2) and dissolution efficiency (DE)
Linear regression equation represented as: y=0.0266x+0.0354; $R^2 = 0.9993$

DISCUSSION

The goal of formulation of a solid dosage form is to reach the desired drug target in the anticipated amount and form, over the specific time frame. The physical and chemical states of the drug determine the

success of this cardinal objective, and are controlled by the overall manufacturing process[18]. The efficacy, safety, and quality assurance of any compressed tablet therefore depend on proper monitoring of these physical, physicochemical and biopharmaceutical parameters[15,19,20].

Different manufacturers employ a variety of excipients, bulking agents and tableting processes and these in part, account for the inter brand variations in the weights of the evaluated brands of Amlodipine tablets. The highest variation was observed for the brand coded AML 08.

The two closely related parameters, hardness and friability, that were tested exhibited some level of discordance in some of the brands. These parameters are both measures of the structural integrity of a tablet and as such its ability to withstand capping, aberration, or breakage under the conditions of packaging, storage, transport and handling before usage. An inverse relationship between these parameters is to be expected, such that a higher hardness to friability ratio connotes a stronger tablet that can better withstand structural damage, loss of active component and eventually a compromise of efficacy[16]. All the tested brands were within the official friability limits for uncoated tablets (<1%). However, of the two brands that failed to meet the breaking force requirements, AML 02 unexpectedly also had very low friability value.

Disintegration is a determinant of the absorption rate and bioavailability of the active component of a tablet, as its fragmentation enables solubilization due to the increased surface contact with the dissolution medium[21.] Considerable evidence shows that the excipients rather than compression force determine the disintegration rate of tablets. The excessive use of excipients such as binders and hydrophobic lubricants or inadequate use of disintegrant may hinder the rapid penetration of disintegration fluid, thereby affecting the dissolution rate of the tablet[15,18,22,23]. This was evident in this study as the brand AML 02, which failed the hardness test, had over one-minute disintegration time compared to the innovator brand AML 01, with six seconds. The brand AML 08, had the highest disintegration time (5:27±1:02) but low breaking force (4.10 KgF), showing that the excipients and not the breaking force, clearly had more effect on disintegration.

The dissolution profiling using the DE, is a viable tool for the batch to batch standardization of manufacturing processes, connotes similarity and is a good predictor of a product's therapeutic activity and bioequivalence[24,25]. Furthermore, the model-independent approach that allows a simple and direct comparison of data in the form of a single value was also used[26,27]. The similarity factor f_2, being a more sensitive parameter than f_1 in detecting divergence in the dissolution curves indicted the closeness between AML 09, AML 03 and the innovator brand AML 01. This was also corroborated by the values obtained from the DE as well as the f_1 values. The observed similarities as derived from the dissolution profile also validate the disintegration time parameters. Although as a Biopharmaceutics Classification System (BCS) class III drug, amlodipine besylate qualifies for a biowaiver, all the brands have not demonstrated pharmaceutical equivalence to the innovator brand, thus making bioequivalence studies imperative in order for healthcare professionals to make appropriate and informed interchangeability decisions.

CONCLUSION

The results of our study indicate that all the brands, except AML 08 and AML 10, satisfied the compendial specifications (USP) and based on the fit factors as well as the DE, the generic brands AML 03 and AML 09 are the closest substitutes of the innovator brand and may be suitable for interchangeability. However, this is subject to performing bioequivalence studies.

Furthermore, it appears that the variations in the dissolution profiles of the other brands from the comparator may also be related to specific formulation processes. Nonetheless, the results of this study highlight the need for constant monitoring and stricter control of approved drugs in the market.

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